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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/593,181

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Helke Hillebrand

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EXAMINER

WORLEY, CATHY KINGDON

ART UNIT

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1638

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/593,181	<b>Applicant(s)</b> HILLEBRAND ET AL.	
	<b>Examiner</b> CATHY K. WORLEY	<b>Art Unit</b> 1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 29 April 2009.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-29 is/are pending in the application.
- 4a) Of the above claim(s) 5-9, 11-26, 28 and 29 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-4, 10 and 27 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 15 September 2006 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>9/15/06</u> .   | 6) <input type="checkbox"/> Other: _____                          |

## DETAILED ACTION

### *Restriction/Election*

1. In response to the communication received on April 29, 2009, Hui-Ju Wu, the election with traverse of group I, claims 2 (part a) and 10, is acknowledged.

The Applicant traverses on the grounds that there is a shared special technical feature which is the use of a D-amino acid oxidase as a positive and negative selection marker in the same cells (see paragraph bridging pages 10-11). This is not persuasive, however, because this technical feature is not required for claims 11-26; therefore, it can not be relied upon for the technical feature that provides unity of invention for the claim set. Furthermore, this property is obvious over the prior art (see rejection under 35 USC 103 (below) and therefore, it lacks an inventive step over the prior art and is not a special technical feature according to PCT Rule 13.2 as it does not define a contribution over the prior art.

The Applicant argues that in order to maintain the transformed plant's ability to utilize D-amino acid as a nitrogen source and grow on media which would not otherwise support growth of the wild-type plant, one skilled in the art would not modify the method taught in Nasholm to include a subsequent step of excising the selection marker from the plant (see last paragraph on page 11). This is not persuasive, however, because one of ordinary skill may want to transfer the plant to

soil in order to grow it outside, and then excising the marker would be appropriate. There is nothing in the instant claims to exclude a method that would include a further step of transferring a plant to soil which is a very common practice in agriculture.

The Applicant argues that the D-amino acid oxidase genes taught in the instant application are not functional equivalents of the hpt gene taught by Dale (see first two paragraphs on page 12). This is not persuasive, however, because the D-amino acid oxidase genes can serve as a selection marker, in very much the same way as the hpt gene; therefore, they are functional equivalents. The fact that they can serve as both positive and negative selection is taught by Nasholm et al, so this is not unexpected.

The Applicant argues that Dale discloses excision of the selection marker using the Cre/lox system, whereas the instant claims are directed toward regeneration of transgenic cells or progeny plants during crossing away of the selection marker. This is not persuasive, however, because the instant claims encompass excision with a recombinase such as Cre/lox (see claim 9).

The Applicant argues that the international search authority found unity of invention; and therefore, the USPTO should also find unity of invention; and that the search has already been conducted by the international search authority so there is no burden (see third paragraph on page 13). This is not persuasive, however, because the USPTO is independent of the international search authority,

and therefore the Examiner makes a determination regarding unity of invention. Furthermore, the Examiner is not allowed to rely on the internal search. The Examiner is required to do an independent search; therefore, there is a burden. It is also noted that the written opinion of the international searching authority states that all claims lacked an inventive step over the prior art, therefore, their opinion is in agreement with that of the Examiner.

2. Elected claims 2 (part a) and 10 will be examined along with linking claims, 1, 3, 4, and 27, in this Office Action. Claims 1-29 are pending. Claims 5-9, 11-16, 28, and 29 are withdrawn from consideration for being directed to non-elected inventions.

### ***Specification***

3. The abstract of the disclosure is objected to because it is not sufficiently descriptive of the invention. The abstract should be between 50 and 150 words in length, and it should specify that plants are transformed with constructs expressing D-amino acid oxidases which can serve as both positive and negative selection markers. Correction is requested. See MPEP § 608.01(b).

4. The title of the invention is not descriptive of the elected invention. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: - - A method for producing a transgenic plant expressing a D-amino acid oxidase which can be used as both a positive and a negative selection marker - - .

5. The use of the trademark, EPPENDORF, has been noted in this application. Trademarks should be written in all capital letters wherever they appear; or alternatively, they should be denoted with the registered trademark symbol, ®, and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

### ***Claim Objections***

6. Claim 2 is objected to because of the following informalities: it continues to recite part “b” which was not elected for prosecution. Because the linking claims

were not found to be allowable, part “b” of claim 2 should be deleted. Appropriate correction is requested.

7. Claim 2 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 2 recites methods for breaking the combination of two expression cassettes, and those can be deletion or excision of an expression cassette or segregation of the two expression cassettes when they were co-transformed rather than being included in a single vector. These are the only ways to break the combination, therefore, claim 2 does not further limit claim 1; because there are no other ways that the combination can be broken.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1, 3, 4, 10, and 27 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. All dependent claims are included in this rejection; with the exception of claim 2 which includes the missing essential steps.

The omitted steps are: the steps that must be taken for “breaking the combination between said first expression cassette and said second expression cassette” as recited in step “v”.

9. Claims 1-4, 10, and 27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to a method that utilizes “compound X” and “compound M” both of which comprise a “D-amino acid structure”. The specification states that a D-amino acid structure is intended to include D-amino acids as well as analogues, derivatives, and mimetics of the D-amino acid that maintain the functional activity of the compound (see last paragraph on page 40 of the specification).



The essential feature of compound X is that it is phytotoxic against plant cells and can be metabolized by a D-amino acid oxidase into one or more compounds which are non-phytotoxic or less phytotoxic than compound X (see part “ii” of claim 1). The essential feature of compound M is that it is non-phytotoxic or moderately phytotoxic against plant cells and can be metabolized by a D-amino acid oxidase into one or more compounds which are phytotoxic or more phytotoxic than compound M (see part “iv” of claim 1).

The Applicants describe D-alanine and D-serine as choices for compound X and D-isoleucine and D-valine as choices for compound Y (see Figure 1; and see first paragraph on page 32).

The Applicants do not describe any D-amino acids other than D-alanine and D-serine that can function as required for compound “X”; and they do not describe any D-amino acids other than D-isoleucine and D-valine that can function as required for compound “M”. The Applicants do not describe any analogues, derivatives, and mimetics of D-amino acids that maintain the functional activity of the compounds.

The Applicants fail to describe a representative number of D-amino acid structures that can function as required for compound X and compound M. The Applicants only describe D-alanine and D-serine for compound X and D-isoleucine and D-valine for compound M. Furthermore, the Applicants fail to describe structural features common to members of the claimed genus of D-amino acid

structures. Hence, Applicants fail to meet either prong of the two-prong test set forth by *Eli Lilly*. Furthermore, given the lack of description of the necessary elements essential for a compound to be phytoxic against plant cells, as required for compound X, and metabolized by a D-amino acid oxidase into one or more compounds which are non-phytoxic or less phytotoxic than compound X (see part “ii” of claim 1), it remains unclear what features identify a D-amino acid structure capable of such activity. Given the lack of description of the necessary elements essential for a compound to be non-phytotoxic or moderately phytotoxic against plant cells, as required for compound M, and metabolized by a D-amino acid oxidase into one or more compounds which are phytotoxic or more phytotoxic than compound M (see part “iv” of claim 1) it remains unclear what features identify a D-amino acid structure capable of such activity. Since the genus of D-amino acid structures that are capable of serving as compound X and compound M has not been described by specific structural features, the specification fails to provide an adequate written description to support the breadth of the claims.

D-amino acid structures can be analogues, derivatives, and mimetics of any D-amino acid (see last paragraph on page 40 of the specification). Therefore the genus of D-amino acid structures encompasses a very large number of molecules, many of which would not have the required phytotoxicity to plants and relief of phytotoxicity after metabolism by D-amino acid oxidase as required by compound X, and most of which were not in the possession of the applicant at the time of filing.

In addition, the genus of D-amino acid structures encompasses a very large number of molecules, many of which would not have the required lack of phytotoxicity and production of phytotoxic metabolite by D-amino acid oxidase activity as required for compound M, and most of which were not in the possession of the applicant at the time of filing. The Applicants have reduced to practice only two compounds for compound X (D-alanine and D-serine – see figure 4) and two compounds for compound M (D-isoleucine and D-valine – see figure 4). Accordingly, the specification fails to provide an adequate written description to support the genus of D-amino acid structures that can function as compound X and compound M as set forth in the claims. (See Written Description guidelines published in 2008 online at <http://www.uspto.gov/web/menu/written.pdf>).

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

10. Claims 1-4, 10, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Signer et al (WO 01/96583; published on Dec. 20, 2001) in view of Nasholm et al (WO 03/060133; published On July 24, 2003) and taken with the

evidence of Stougaard, J. (The Plant Journal (1993) Vol. 3; pp. 755-761) and the evidence of Boeke et al (Methods in Enzymology (1987) Vol. 154; pp. 164-175).

The claims are directed to a method for producing a transgenic plant by transforming a plant cell with a nucleic acid encoding a D-amino oxidase and with a second nucleic acid conferring an agronomically valuable trait, and utilizing D-amino acid structures for both a positive selection step and a negative selection step, followed with breaking the combination between the two nucleic acids.

Signer et al teach a method of generating transgenic plants that utilizes both a positive selection marker and a negative selection marker in order to remove the selection markers from the resulting transgenic plants (see entire document). They outline a general protocol on page 11:

- 1) providing a DNA construct which comprises (a) direct repeats of a gene of interest at both ends flanking a positive selectable marker gene and a negative selectable marker gene and (b) one or more additional genes that flank either side or both sides of (a);
- 2) transforming cells by introducing the construct into the cells;
- 3) growing or culturing the cells on positive selective medium;
- 4) selecting the transformed cells having the genetic construct which grows on the positive selective medium;
- 5) transferring the cells to a negative selective medium;
- 6) growing or culturing the cells on the negative selective medium;

And

- 7) selecting those cells which grow on the negative selective medium.

Growth on the negative selective medium indicates that the selection markers have been excised.

Signer et al do not teach a sequence encoding a D-amino acid oxidase gene for use as either a positive or a negative selection marker.

Nasholm et al teach that D-amino acids may be used for selection of transgenic plants expressing a D-amino acid metabolizing protein (see page 3). They teach that the D-amino acid metabolizing protein can be a D-amino acid oxidase (see line 21 on page 5). They teach that D-amino acid oxidase could be used as a positive selection marker with D-alanine and D-serine because D-amino acid oxidase would alleviate the toxicity caused by D-alanine and D-serine (see fourth paragraph on page 35). They also teach that D-amino acid oxidase could be used as a negative selection marker with D-isoleucine because applying D-isoleucine to plants expressing D-amino acid oxidase hindered the growth of the transgenic plant with no visible inhibitory effect on wild type plants (see first paragraph on page 36).

At the time the invention was made, it would have been obvious and within the scope of one of ordinary skill in the art to modify the teachings of Signer et al to utilize a D-amino acid oxidase as taught by Nasholm et al. One would have been motivated to do so, because Nasholm et al taught that one transgene (encoding D-amino acid oxidase) could be useful as both a positive and a negative selection

marker, and therefore one would only require one transgene rather than two separate selectable marker genes.

This concept was generally known in the art as evidenced by the teachings of Stougaard (see entire article) and Boeke et al (see entire article). Stougaard teaches transgenic tobacco expressing a transgene encoding CodA which can be used for positive selection on N-(phosphonacetyl)-L-aspartate containing medium and can be used for negative selection on 5-fluorocytosine containing medium (see abstract). Boeke et al teach that the URA3 gene can be used in yeast as both a positive selectable marker and as a negative selectable marker (see figure 1 on page 166). It is common practice in yeast genetics to use a plasmid comprising the URA3 gene as a positive selectable marker by growing URA3<sup>-</sup> yeast on medium lacking uracil, therefore only the transformants carrying the URA3 gene are able to grow (positive selection). For a negative selection, the yeast would be plated on medium containing 5-FOA (5-fluoroorotic acid) (see Figure 1 on page 166).

Given the effect of different D-amino acids on transgenic plants expressing D-amino acid oxidase as taught by Nasholm et al, and given the success in using both a positive selection and negative selection to produce transgenic plants and subsequently excise the markers that was taught by Signer et al, one would have had a reasonable expectation of success in combining the teaching to arrive at a method that utilizes D-amino acid oxidase as both a positive and negative selectable marker, as claimed in the instant application.

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cathy K. Worley whose telephone number is (571) 272-8784. The examiner is on a variable schedule but can normally be reached on M-F 10:00 - 4:00 with additional variable hours before 10:00 and after 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg, can be reached on (571) 272-0975. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Cathy K. Worley/  
Primary Examiner, Art Unit 1638